REMARKS/ARGUMENTS

Claims 1 to 8, 14 to 17, and 24 are pending in the application. Claims 1, 2, and 14 to 17 have been amended, herein, and no claims have been cancelled or added.

Applicant respectfully requests reconsideration of the rejections of record in view of the foregoing amendments and the following remarks.

I. Alleged Anticipation

Claims 1 to 7, 14 to 17, and 24 have been rejected under 35 U.S.C. § 102(a or b) as allegedly anticipated by Tsutsumi, Y., *et al.*, *British J. Cancer* 74:1090-1095 (1996) (hereinafter "the Tsutsumi I reference"). Applicant respectfully traverses the rejection because the reference fails to teach or suggest every limitation of the amended claims. The Tsutsumi I reference describes human tumor necrosis factor-α covalently modified with polyethylene glycol of average molecular weights of 2,000; 5,000; or 12,000. Claims 1 and 14 have been amended to recite modified TNF comprising TNF covalently bound to PEG molecules having an approximate weight average molecular weight in the range of 15,000 to about 40,000, and methods of enhancing the circulating half life of TNF while reducing its toxicity comprising modifying TNF by covalently bonding to it PEG molecules having an approximate weight average molecular weight in the range of 15,000 to about 40,000, respectively. Claims 2, 15, and 17 have been amended to delete the word "about" before 20,000. Support for the amendments is found throughout the specification as originally filed and at, for example, page 7, lines 3 to 8 and Example 3. The Tsutsumi I reference fails to teach or suggest tumor necrosis factor covalently bound to PEG molecules having an approximate weight average molecular weight in the range of 15,000 to about 40,000 and,

therefore, fails to teach or suggest every limitation of the present claims. Applicants accordingly, respectfully request withdrawal of the rejection.

II. Alleged Obviousness

A. Claims 1 and 8 have been rejected under 35 U.S.C. § 103(a) as allegedly obvious over the Tsutsumi I reference in view of Mark, D.F., *et al., Methods Enzymol.* 154: 403- 414 (1987) (hereinafter "the Mark reference"). Applicant respectfully traverses the rejection because the Tsutsumi I and Mark references fail to teach or suggest every limitation of the amended claims.

To establish *prima facie* obviousness, the PTO must satisfy three requirements. First, the Patent Office must provide objective evidence that the prior art relied upon, coupled with the knowledge generally available in the art at the time of the invention, contains some suggestion or incentive that would have motivated those of ordinary skill in the art to modify a reference or to combine references. *In re Lee*, 61 U.S.P.Q.2d 1430, 1433 (Fed. Cir. 2002); *In re Fine*, 837 F.2d 1071, 1074, 5 U.S.P.Q.2d 1596, 1598 (Fed. Cir. 1998). Second, the proposed modification or combination of the prior art must have had a reasonable expectation of success, determined from the vantage point of those of ordinary skill in the art, at the time the invention was made. *Amgen, Inc. v. Chugai Pharm. Co.*, 927 F.2d 1200, 1209, 18 U.S.P.Q.2d 1016, 1023 (Fed. Cir. 1991). Finally, the prior art reference or combination of references must teach or suggest all the limitations of the claims. *In re Wilson*, 424 F.2d 1382, 1385, 165 U.S.P.Q. 494, 496 (C.C.P.A. 1970).

Assuming *arguendo* that those of ordinary skill in the art would have been motivated to combine the teachings of the Tsutsumi I and Mark references, which Applicant does not

concede, the combination fails to teach or suggest every limitation of the amended claims. As previously discussed, claim 1 has been amended to recite modified TNF comprising TNF covalently bound to PEG molecules having an approximate weight average molecular weight in the range of 15,000 to about 40,000, and the Tsutsumi I reference fails to teach or suggest TNF covalently bound to polyethylene glycol of this molecular weight. The Mark reference fails to overcome the deficiencies of the Tsutsumi I reference. For example, the Mark reference describes amino-terminal deletion mutants of tumor necrosis factor. Specifically, the reference describes deletion mutants of TNF in which either the first nine or the first ten amino acids of the polyepeptide have been removed. The reference fails to teach or suggest covalently binding the TNF deletion mutants to polyethylene glycol, much less binding the mutants to polyethylene glycol of a weight average molecular weight of 15,000 to about 40,000. The Tsutsumi I and Mark references, therefore, when considered alone or in combination, fail to teach or suggest every limitation of the amended claims. Applicant accordingly, respectfully requests withdrawal of the rejection.

B. Claims 1 to 7, 14 to 17, and 24 have been rejected under 35 U.S.C. § 103(a) as allegedly obvious over Tsutsumi, Y., *et al., Jpn J. Cancer Res.* 85:9-12 (1994)(hereinafter "the Tsutsumi II reference") in view of Satake-Ishikawa, R., *et al., Cell Structure and Function* 17:157-160 (1992)(hereinafter "the Satake-Ishikawa reference") and EP 0 401 384 (hereinafter "the Ishikawa application"). Applicant respectfully traverses the rejection because the Office Action has failed to establish *prima facie* obviousness.

Significantly, the Office Action has failed to make of record ***any actual evidence*** of a motivation, teaching, or suggestion that would have led persons of ordinary skill in the art to combine the teachings of the Ishikawa application with those of the Tsutsumi II and Satake-

Ishikawa references. In fact, those of ordinary skill in the art would *not* have been motivated to combine the teachings of the Ishikawa application with those of the Tsutsumi II and Satake-Ishikawa references because the references fail to make any suggestion whatsoever as to the desirability of the combination. For example, the Tsutsimi II reference describes human tumor necrosis factor-α chemically modified with polyethylene glycol of a weight average molecular weight of 5,000. (See page 9). The reference fails to teach or suggest the desirability of modifying tumor necrosis factor-α with polyethylene glycol of a molecular weight greater than 5,000. The Satake-Ishikawa reference describes the preparation and testing of human granulocyte colony-stimulating factor (rHuG-CSF) modified with polyethylene glycol of molecular weights of 4,500 or 10,000, and states that rHuG-CSF modified with polyethylene glycol of a molecular weight of 10,000 exhibited a higher *in vivo* activity than did rHuG-CSF modified with polyethylene glycol of a molecular weight of 4,500. (See page 157 and 159). The reference makes no teaching or suggestion whatsoever, however, with respect to what effect modifying rHuG-CSF with polyethylene glycol of a molecular weight higher than 10,000 would have and, accordingly, fails to teach or suggest the desirability of modifying rHuG-CSF with polyethylene glycol of a molecular weight greater than 10,000.

The Ishikawa application describes the preparation and testing of rHuG-CSF modified with polyethylene glycol of molecular weights of 4,000, 4,500 or 10,000, and states that "[a] molecular weight of the polyethylene glycol used in the present invention is not restricted to any particular range, being, however, normally of from 500 - 20,000 and preferably of from 4,000 - 10,000." (See page 5, lines 24 to 27). The reference only describes the production and testing of rHuG-CSF modified with PEG of molecular weights of 4,000, 4,500 or 10,000,

however, and does not teach or describe the preparation rHuG-CSF modified with PEG of molecular weights greater than 10,000. Significantly, the reference provides no teaching or suggestion whatsoever as to what effect modifying rHuG-CSF, or any polypeptide, with polyethylene glycol of a molecular weight greater than 10,000 would have, much less suggest the desirability of producing polypeptides modified with polyethylene glycol of such molecular weights.

Accordingly, based on the references cited in the Office Action, those of ordinary skill in the art would *not* have been motivated to produce polypeptides modified with polyethylene glycol of molecular weights greater than 10,000 because the references fail to teach or suggest the desirability or advantages of doing so. "The mere fact that references can be combined or modified does not render the resultant combination obvious ***unless the prior art also suggests the desirability of the combination***." M.P.E.P. § 2143.01 citing *In re Mills*, 916 F.2d 680 (Fed. Cir. 1990) (emphasis added). Accordingly, those of ordinary skill in the art would not have been motivated to combine the teachings of the Ishikawa application with those of the Tsutsumi II and Satake-Ishikawa references, and, significantly, the Office Action has failed to offer any evidence to the contrary.

Moreover, those of ordinary skill in the art would not have reasonably expected that polypeptides, including tumor necrosis factor, could have been successfully conjugated to polyethylene glycol of molecular weights greater than 10,000 due to the failure of the cited references to teach or suggest the effects of modifying polypeptides with polyethylene glycol of these molecular weights. As previously discussed, the Tsutsimi II reference describes human tumor necrosis factor-α chemically modified with polyethylene glycol of a weight average molecular weight of 5,000, and the Satake-Ishikawa reference and Ishikawa

application describe rHuG-CSF modified with polyethylene glycol having molecular weights of 4,500 or 10,000 and molecular weights of 4,000, 4,500, or 10,000, respectively. The cited references thus provide no guidance whatsoever as to the effect that modifying a polypeptide with polyethylene glycol of a molecular weight greater than 10,000 would have on the activity and properties of the polypeptide. Accordingly, those of ordinary skill in the art would not have reasonably expected that polypeptides such as tumor necrosis factor could have been successfully modified with PEG of molecular weights greater than 10,000. Those of ordinary skill in the art, therefore, would not have had a reasonable expectation of success for combining the teachings of the Ishikawa application with those of the Tsutsumi II and Satake-Ishikawa references, and, importantly, the Office Action has failed to offer any evidence to the contrary. The Office Action has therefore failed to establish *prima facie* obviousness, and Applicant respectfully requests withdrawal of the rejection.

C. Claims 1 and 8 have been rejected under 35 U.S.C. § 103(a) as allegedly obvious over the Tsutsumi II reference in view of the Satake-Ishikawa reference and the Ishikawa application and further in view of the Mark reference. Applicant respectfully traverses the rejection as it appears to be based on the assumption that those of ordinary skill in the art would have been motivated to combine the teachings of the Tsutsumi II reference with those of the Satake-Ishikawa reference and the Ishikawa application. Because this assumption is believed to be incorrect, as discussed above, Applicant respectfully requests withdrawal of the rejection.

III. Alleged Lack of Enablement

Claims 1 to 8, 14 to 17, and 24 have been rejected under 35 U.S.C. § 112, first paragraph for alleged lack of enablement. The Office Action asserts that the specification is "enabling for modification of TNF-α with PEG having an approximate weight average molecular weight in the range of 10,000 to about 40,000, [but] does not reasonably provide enablement for modification of TNF-α with 5-12 PEG molecules having an approximate weight average molecular weight in the range of 10,000 to about 40,000." (Office Action dated July 14, 2003, page 11). Without conceding the correctness of the assertion, and to advance prosecution, claims 1, 14, and 16 have been amended to no longer recite the number of PEG molecules to which the TNF is bound, and to recite, *inter alia*, modified TNF covalently bound to PEG having an approximate weight average molecular weight in the range of 15,000 to about 40,000. Support for the amendments is found throughout the specification as originally filed. As acknowledged in the Office Action, the specification enables those of ordinary skill in the art to make and use the full scope of the subject matter defined by the amended claims. Applicant accordingly, respectfully requests withdrawal of the rejection.

IV. Alleged Indefiniteness

Claims 1 to 4, 14 to 17, and 24 have been rejected under 35 U.S.C. § 112, second paragraph as allegedly indefinite for recitation of the term "TNF." Applicant respectfully traverses the rejection because the cited term conveys a clear and definite meaning to those skilled in the art.

"The test for definiteness is whether one skilled in the art would understand the bounds of the claim when read in light of the specification. If the claims read in light of the specification reasonably apprise those skilled in the art of the scope of the invention, § 112 [second paragraph] demands no more." *Miles Laboratories, Inc. v. Shandon Inc.*, 997 F.2d 870, 875 (Fed. Cir. 1993). Definiteness of claim language must be analyzed, not in a vacuum, but in light of the content of the particular application disclosure, the teachings of the prior art, and the claim interpretation that would be given by one possessing the ordinary level of skill in the pertinent art at the time the invention was made. *In re Moore*, 439 F.2d 1232, 1235 (C.C.P.A. 1971); M.P.E.P. § 2173.02. When the present claim language is so examined, it becomes apparent that those of ordinary skill in the art would understand the meaning of the term "TNF." The specification defines the terms "tumor necrosis factor" and "TNF" using clear and unambiguous language that would be readily understood by those skilled in the art. See, for example, page 5, line 23 to page 6, line 5 of the specification as filed. Accordingly, upon review of the specification, those skilled in the art could identify the subject matter encompassed by the term "TNF" and could thus easily ascertain the metes and bounds of the claims.

Although the Office Action asserts that "the specification does not identify that material element or combination of elements which is unique to, and, therefore, definitive of 'TNF'" (Office Action dated July 14, 2003, page 13), the second paragraph of section 112 contains no such requirement. The second paragraph of section 112 requires that the claims read in light of the specification reasonably apprise those skilled in the art of the scope of the invention, and does not require the specification to identify an element or combination of elements that is unique to any particular claim term. As discussed above, the specification

clearly defines the term "TNF" and unambiguously identifies the subject matter encompassed by the term. The requirements of the second paragraph of section 112 have therefore been met, and Applicant accordingly, respectfully requests withdrawal of the rejection.

V. Claim Objections

Claim 17 has been objected to under 37 C.F.R. § 1.75(c) as being of improper dependent form for allegedly failing to further limit the subject matter of a previous claim. The Office Action asserts that a molecule having an approximate weight average molecular weight in the range of about 20,000 to about 30,000 does not further limit a molecule having an approximate molecular weight in the range of 20,000 to 30,000. Without conceding the correctness of the assertion, and to advance prosecution, claim 17 has been amended to delete both instances of the word "about," obviating the objection. Applicant accordingly, respectfully requests withdrawal thereof.

Conclusion

Applicants believe that the foregoing constitutes a complete and full response to the Office Action of record. Accordingly, an early and favorable Action is respectfully requested.

Respectfully submitted,

Date: October 14, 2003

Jane E. Inglese, Ph.D.
Registration No. 48,444

Woodcock Washburn LLP
One Liberty Place - 46th Floor
Philadelphia PA 19103
Telephone: (215) 568-3100
Facsimile: (215) 568-3439